CLAIMS

What is claimed is:

1. A variant of a protein comprising amino acid residues Cys^{37} to Ser^{208} of SEQ ID NO:2 (KGF-2), said variant selected from the group consisting of a variant comprising ΔN41 KGF-2, ΔN40 KGF-2, ΔN39 KGF-2, ΔN38 KGF-2, ΔN37 KGF-2, ΔN36 KGF-2 and ΔN35 KGF-2, or R_1-[Asn^{71}-Pro^{203}]-COOH proteins, wherein [Asn^{71}-Pro^{203}] represents residues 71 through 203 of SEQ ID NO:2; wherein R_1 represents a methionylated or nonmethionylated amine group of Asn^{71} or of amino-terminus amino acid residue(s) of:

Tyr
Ser-Tyr
Arg-Ser-Tyr
Val-Arg-Ser-Tyr (SEQ ID NO:9),
His-Val-Arg-Ser-Tyr, (SEQ ID NO:10),
Arg-His-Val-Arg-Ser-Tyr (SEQ ID NO:11),
Gly-Arg-His-Val-Arg-Ser-Tyr (SEQ ID NO:12),
Ala-Gly-Arg-His-Val-Arg-Ser-Tyr (SEQ ID NO:13),
Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr (SEQ ID NO:14),
Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr
(SEQ ID NO:15),
Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr
(SEQ ID NO:16),
Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr
(SEQ ID NO:17),
Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr
(SEQ ID NO:18),
Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr
(SEQ ID NO:19),

Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr (SEQ ID NO:20),
Ser-Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr (SEQ ID NO:21),
Ser-Ser-Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr (SEQ ID NO:22),
Ser-Ser-Ser-Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr (SEQ ID NO:23),
Ser-Ser-Ser-Ser-Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr (SEQ ID NO:24),
Asn-Ser-Ser-Ser-Ser-Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr (SEQ ID NO:25),
Thr-Asn-Ser-Ser-Ser-Ser-Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr (SEQ ID NO:26),
Ala-Thr-Asn-Ser-Ser-Ser-Ser-Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr (SEQ ID NO:27),
Glu-Ala-Thr-Asn-Ser-Ser-Ser-Ser-Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr
(SEQ ID NO:28),
Pro-Glu-Ala-Thr-Asn-Ser-Ser-Ser-Ser-Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr
(SEQ ID NO:29),
Ser-Pro-Glu-Ala-Thr-Asn-Ser-Ser-Ser-Ser-Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr
(SEQ ID NO:30),
Val-Ser-Pro-Glu-Ala-Thr-Asn-Ser-Ser-Ser-Ser-Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr
(SEQ ID NO:31),
Met-Val-Ser-Pro-Glu-Ala-Thr-Asn-Ser-Ser-Ser-Ser-Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr
(SEQ ID NO:32),
Asp-Met-Val-Ser-Pro-Glu-Ala-Thr-Asn-Ser-Ser-Ser-Ser-Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr
(SEQ ID NO:33),

Gln-Asp-Met-Val-Ser-Pro-Glu-Ala-Thr-Asn-Ser-Ser-Ser-Ser-Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr (SEQ ID NO:34),
Gly-Gln-Asp-Met-Val-Ser-Pro-Glu-Ala-Thr-Asn-Ser-Ser-Ser-Ser-Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr (SEQ ID NO:35),
Leu-Gly-Gln-Asp-Met-Val-Ser-Pro-Glu-Ala-Thr-Asn-Ser-Ser-Ser-Ser-Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr (SEQ ID NO:36),
Ala-Leu-Gly-Gln-Asp-Met-Val-Ser-Pro-Glu-Ala-Thr-Asn-Ser-Ser-Ser-Ser-Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr (SEQ ID NO:37),
Gln-Ala-Leu-Gly-Gln-Asp-Met-Val-Ser-Pro-Glu-Ala-Thr-Asn-Ser-Ser-Ser-Ser-Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr (SEQ ID NO:38), or
Cys-Gln-Ala-Leu-Gly-Gln-Asp-Met-Val-Ser-Pro-Glu-Ala-Thr-Asn-Ser-Ser-Ser-Ser-Ser-Phe-Ser-Ser-Pro-Ser-Ser-Ala-Gly-Arg-His-Val-Arg-Ser-Tyr (SEQ ID NO:39),

and, wherein R_2 represents a carboxy group of Pro^{203} or of carboxy-terminal amino acid residues of:

Met
Met-Val
Met-Val-Val
Met-Val-Val-His (SEQ ID NO:40),
or
Met-Val-Val-His-Ser (SEQ ID NO:41),

<u>provided however</u>, that R_1 and R_2 are not selected so as to reconstruct Cys^{37} to Ser^{208} of SEQ ID NO:2;

a variant comprising at least one amino acid residue within Asn^{168} to Met^{176} of SEQ ID NO:2 being deleted or substituted with a non-native amino acid;

a variant comprising at least one non-native amino acid being added within Asn^{168} to Met^{176} of SEQ ID NO:2, and chemical derivatives thereof;

a variant comprising at least one neutral or positively charged amino acid residue within amino acids 85-198 of SEQ ID NO:2 being deleted or substituted with a neutral residue or negatively charged residue, whereby a charge-change protein with reduced positive charge is generated, and chemical derivatives thereof;

a variant comprising the substitution of at least one amino acid residue having a higher loop forming potential for an amino acid having a lower loop forming potential within a putative loop-forming region of amino acid residues 160-164 of SEQ ID NO:2, and chemical derivatives thereof;

a variant comprising at least one naturally-occurring cysteine at position 37, 106 or 150 of SEQ ID NO:2 being deleted or substituted with a non-native amino acid residue, and chemical derivatives thereof;

a variant comprising at least one amino acid within an N-linked or O-linked glycosylation site being deleted or substituted with a non-native amino acid, whereby the N-linked or O-linked glycosylation site is modified, and derivatives thereof;

a variant comprising the addition or substitution of at least one non-native amino acid to generate an N-linked or O-linked glycosylation site, and chemical derivatives thereof; and

a variant comprising a C-terminal addition of at least one domain of the constant region of a heavy chain of a human immunoglobulin, and chemical derivatives thereof.

2. The variant of KGF-2 according to Claim 1, selected from the group consisting of ΔN36 KGF-2,

ΔN35 KGF-2, ΔN34 KGF-2, ΔN33 KGF-2, ΔN32 KGF-2, ΔN31 KGF-2 and ΔN30 KGF-2, and chemical derivatives thereof.

3. The variant of KGF-2 according to Claim 1, wherein NH_2-Ala-Lys-Trp-Thr-His-Asn-Gly-Gly-Glu-Met-COOH is substituted for residues within Asn^{168} to Met^{176} of SEQ ID NO:2.

4. The variant of KGF-2 according to Claim 1, wherein residues Thr^{86}, Gly^{182}, Arg^{187} or Asn^{196} of SEQ ID NO:2 are substituted with a non-native amino acid.

5. The variant of KGF-2 according to Claim 4, wherein the amino acids are alanine, glutamic acid, aspartic acid, glutamine, asparagine, glycine, valine, leucine, isoleucine, serine and threonine.

6. The variant of KGF-2 according to any one of Claims 1 through 5, wherein said amino acid sequence is nonglycosylated.

7. The variant of KGF-2 according to any one of Claims 1 through 5, wherein said amino acid sequence is glycosylated.

8. A chemical derivative comprising a water soluble polymer conjugated to a variant of KGF-2 according to any one of Claims 1 through 7.

9. A chemical derivative comprising a water soluble polymer conjugated to a KGF-2 comprising amino acid residues Cys^{37} to Ser^{208} of SEQ ID NO:2 (KGF-2).

10. A polynucleotide encoding the variant of KGF-2 according to any one of Claims 1 through 7.

11. A vector comprising a polynucleotide of Claim 10 operatively linked to an expression control sequence.

12. A prokaryotic or eukaryotic host cell containing a polynucleotide of Claim 10.

13. A method comprising growing host cells of Claim 12 in a suitable nutrient medium and, optionally, isolating said variant of KGF-2 from said cells or said nutrient medium.

14. The method for producing the variant of KGF-2 according to Claim 13, wherein said host cells are *E. coli*.

15. The method for producing the variant of KGF-2 according to Claim 13, wherein said host cells are selected from baculovirus cells, COS cells and Chinese hamster ovary cells.

16. A method comprising the step of isolating a variant of KGF-2 from a host cell containing a polynucleotide of Claim 10 cultured under conditions allowing the expression of the variant of KGF-2 by said host cell.

17. The method according to Claim 16 comprising the step of modifying the isolated variant of KGF-2 to generate a compound capable of stimulating the production of epithelial cells.

18. A method comprising the steps of:

(a) culturing a prokaryotic or eukaryotic host cell containing a polynucleotide of Claim 10;

(b) maintaining said host cell under conditions allowing the expression of a variant of KGF-2 by said host cell; and

(c) optionally isolating the variant of KGF-2 expressed by said host cell.

19. The variant of KGF-2 according to Claim 1 which is the recombinant expression product of a prokaryotic or eukaryotic host cell containing an exogenous polynucleotide of Claim 10.

20. A pharmaceutical composition comprising the variant of KGF-2 according to any one of Claims 1 through 7 in association with a pharmaceutically acceptable vehicle.

21. A pharmaceutical composition comprising the variant of KGF-2 produced in accordance with the method of Claim 13 in association with a pharmaceutically acceptable vehicle.

22. A pharmaceutical composition comprising the variant of KGF-2 produced in accordance with the method of Claim 18 in association with a pharmaceutically acceptable vehicle.

23. A method of stimulating the production of epithelial cells comprising contacting such cells with an effective amount of the variant of KGF-2 according to Claims 1 through 7.

24. A method of stimulating the production of epithelial cells comprising contacting such cells with

an effective amount of the chemical derivative according to Claims 8 through 9.

add B27

add D4